

Appl. No. 10/033,303  
Amdt. dated September 13, 2005  
Reply to Office Action of March 9, 2005 and the Notice of  
Non-Compliant Amendment mailed August 25, 2005

PATENT

**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings of claims in the application.

**Listing of Claims:**

1. (Currently Amended) A machine implemented method for deriving a sequence of at least a portion of an oligomer from a mass spectrum data of fragments of said oligomer, said method comprising:  
~~providing a predetermined~~ calculating a set of mass/charge (m/z) values for monomer sequences thereby producing a calculated set of mass/charge (m/z) values;  
determining an abundance value from said mass spectrum data for each (m/z) value in said ~~predetermined~~ calculated set, thereby producing a plurality of abundance values;  
calculating a first ranking, based on said plurality of abundance values, for each sequence of a set of fragment sequences having a first number of monomers;  
calculating a second ranking, based on said plurality of abundance values, for each sequence of a set of fragment sequences having a second number of monomers;  
calculating a cumulative ranking, based on said first rang and said second ranking, for each sequence of a set of fragment sequences having at least said second number of monomers.
2. (Currently Amended) A method as in claim 1 wherein said oligomer is ~~a protein~~ is selected from protein, oligonucleotide, oligosaccharide, lipid, and synthetic polymer.
3. (Currently Amended) A method as in claim ~~2~~ 1 wherein said portion of said ~~protein~~ oligomer is a terminal portion of said ~~protein~~ oligomer.
4. (Cancelled)
5. (Original) A method as in claim 3 wherein a label is attached to said portion.

Appl. No. 10/033,303

PATENT

Amdt. dated September 13, 2005

Reply to Office Action of March 9, 2005 and the Notice of  
Non-Compliant Amendment mailed August 25, 2005

6. (Currently Amended) A method as in claim 5 wherein said label is covalently bonded to said ~~protein-oligomer~~ prior to generating said mass spectrum data and wherein said mass spectrum data is transformed from an output of a detector ~~plate~~.

7. (Currently Amended) A method as in claim 6 wherein said ~~protein oligomer~~ is fragmented by collision-induced dissociation to generate fragments, comprising said portion, which are then accelerated toward ~~[[a]] said~~ detector ~~plate~~ to generate said mass spectrum data.

8. (Currently Amended) A method as in claim 3 wherein said ~~protein oligomer~~ is fragmented to generate fragments, comprising said portion, ~~where~~ wherein said fragments are then accelerated toward a detector ~~plate~~ to generate said mass spectrum data.

9. (Currently Amended) A method as in claim 2 wherein said ~~protein oligomer~~ is isolated from other ~~proteins-oligomers~~ extracted from a sample and wherein said machine which implements said method comprises a digital processing system which executes computer programming instructions.

10. - 12. (Cancelled)

13. (Currently Amended) A machine implemented method for deriving a sequence of at least a portion of an oligomer from a mass spectrum data, said method comprising:

~~providing a predetermined~~ calculating a set of mass/charge ( $m/z$ ) values for monomer sequences each of which comprises a mass label thereby producing a calculated set of mass/charge ( $m/z$ ) values;

determining an abundance value from said mass spectra data for each  $m/z$  value in said ~~predetermined~~ calculated set, thereby producing a plurality of abundance values;

calculating a first ranking, based on said plurality of abundance values, for each sequence of a set of monomer sequences having a first number of monomers.

14. (Currently Amended) A method as in claim 13 wherein said oligomer is ~~a protein~~ is selected from protein, oligonucleotide, oligosaccharide, lipid, and synthetic polymer.

Appl. No. 10/033,303

PATENT

Amdt. dated September 13, 2005

Reply to Office Action of March 9, 2005 and the Notice of  
Non-Compliant Amendment mailed August 25, 2005

15. (Currently Amended) A method as in claim 13 wherein said mass label has a mass which is different than a mass of each possible ~~amino-acid~~ monomer in said set of ~~amino-acid~~ monomer sequences.

16. (Currently Amended) A method as in claim 13 wherein said mass label imparts a unique mass signature to each sequence of said set of ~~amino-acid~~ monomer sequences.

17. (Currently Amended) A method as in claim 13 wherein said portion is a terminal portion of said ~~protein~~ oligomer.

18. (Cancelled)

19. (Currently Amended) A method as in claim ~~18~~ 17 wherein said mass label is covalently bonded to said terminal portion prior to generating said mass spectrum data.

20. (Currently Amended) A method as in claim 19 wherein said ~~protein~~ oligomer is fragmented in a mass spectrometer to generate fragments, comprising said portion, which are then accelerated toward a detector ~~plate~~ to generate said mass spectrum data.

21. (Currently Amended) A method as in claim 20 wherein said ~~protein~~ oligomer is isolated from other ~~proteins~~ oligomers extracted from a sample and wherein said machine which implements said method comprises a digital processing system which executes computer programming instructions.

22. - 24. (Cancelled)

25. (Currently Amended) A method as in claim 2 wherein said method is performed for each ~~protein~~ oligomer in a set of ~~proteins~~ oligomers extracted from a biological material and wherein said set of ~~proteins~~ oligomers is more than 100 different ~~proteins~~ oligomers.

26. (Currently Amended) A method as in claim 14 wherein said method is performed for each ~~protein~~ oligomer in a set of ~~proteins~~ oligomers extracted from a biological material and wherein said set of ~~proteins~~ oligomers is more than 100 different ~~proteins~~ oligomers.

27. - 66. (Cancelled)

Appl. No. 10/033,303

PATENT

Amdt. dated September 13, 2005

Reply to Office Action of March 9, 2005 and the Notice of  
Non-Compliant Amendment mailed August 25, 2005

67. (Currently Amended) A method for determining a sequence of at least one portion of an oligomer from mass spectrum data, said method comprising:

reading mass spectrum data in a first reading operation from a non-volatile storage device to a temporary volatile cache memory to obtain abundance values at a set of possible mass/charge ( $m/z$ ) values from said temporary volatile cache memory and calculating first abundance parameters from said abundance values;

reading said mass spectrum data in a second reading operation, following said first reading operation, from said temporary volatile cache memory to obtain said abundance values at said set of possible  $m/z$  values, and determining a ranking, based on said abundance values and said first abundance parameters, for each sequence of a set of monomer sequences having a first number of monomers.

68. (Currently Amended) A method as in claim 67 wherein said oligomer is a protein selected from protein, oligonucleotide, oligosaccharide, lipid, and synthetic polymer.

69. (Original) A method as in claim 68 wherein said first abundance parameters and said ranking for said each sequence are stored in said temporary volatile cache memory.

70. (Original) A method as in claim 68 wherein said set of possible  $m/z$  values is calculated as needed rather than stored on said non-volatile storage device.

71. (Currently Amended) A method as in claim 69 ~~wherein said ranking for each of said sequence is determined from said first abundance parameters and said abundance values obtained in said second reading operation, and~~ wherein said temporary volatile cache memory comprises at least one of an L1 and an L2 cache of a microprocessor.

72. (Original) A machine implemented method for determining a sequence of at least one portion of an oligomer from mass spectrum data, said method comprising:  
determining a first molecular weight for a first monomer sequence;

Appl. No. 10/033,303  
Amdt. dated September 13, 2005  
Reply to Office Action of March 9, 2005 and the Notice of  
Non-Compliant Amendment mailed August 25, 2005

**PATENT**

determining a set of weight adjustments for possible ion types of said first monomer sequence;

determining a set of charge state adjustments for possible charge states of said possible ion types;

calculating a set of m/z values for said first monomer sequence from said first molecular weight, said set of weight adjustments and said set of charge state adjustments.

73. (Currently Amended) A method as in claim 72 wherein said oligomer is a protein selected from protein, oligonucleotide, oligosaccharide, lipid, and synthetic polymer.

74. (Original) A method as in claim 73 wherein said set of m/z values are used to perform lookup operation into a mass spectrum data to obtain abundance values and wherein said set of m/z values are not retained in a non-volatile storage device for access in an abundance value lookup operation.

75. (Original) A method as in claim 74 wherein said set of m/z values is stored in a temporary volatile cache memory when needed and is erased for subsequent lookup operations in said temporary volatile cache memory.

76. (Original) A method as in claim 75 wherein said mass spectrum data is stored in said temporary cache memory.

77. (Original) A method as in claim 76 wherein said temporary volatile cache comprises at least one of an L1 or L2 cache of a microprocessor.

78. (Original) A method as in claim 1 wherein said mass spectrum is digitally filtered to minimize spectral noise prior to said determining said abundance value.

79. (Original) A method as in claim 1 wherein said providing of said predetermined set is one of (a) storing said predetermined set or (b) calculating needed portions of said predetermined set on an as-needed basis.

Appl. No. 10/033,303

PATENT

Amdt. dated September 13, 2005

Reply to Office Action of March 9, 2005 and the Notice of  
Non-Compliant Amendment mailed August 25, 2005

80. (Currently Amended) A method as in claim 1 wherein said ~~protein~~ oligomer is cleaved by collision induced dissociation, either in-source or in a collision cell to generate fragments which are then accelerated toward a detector plate.

81. (Currently Amended) A machine implemented method for deriving a sequence of at least the labeled terminal portion of a ~~protein~~ an oligomer from a mass spectrum data, said method comprising:

labeling the ~~protein~~ oligomer with at least two labels that differ in mass from each other by at least 1 amu;

determining the set of mass/charge (m/z) values for ~~all~~ possible contiguous labeled ~~peptide~~ oligomer fragments that might result from random cleavages of the ~~peptide~~ oligomer backbone;

determining an abundance value from said mass spectrum data for each m/z value in said predetermined set, thereby producing a plurality of abundance values;

calculating a first ranking of the possible sequences for the second label at each ~~residue~~ monomer length by their relative abundances, based on said plurality of abundance values;

calculating a second ranking of the possible sequences for the second label at each ~~residue~~ monomer length by their relative abundances, based on said plurality of abundance values;

calculating a combined ranking for each sequence by linear combination of the first and second rankings at each ~~sequence~~ monomer length; and

calculating a cumulative ranking for the maximum ~~sequence~~ monomer length based on a linear combination of said combined rankings for each ~~residue~~ monomer length of a set of ~~amino acid~~ monomer sequences of the maximum desired ~~sequence~~ monomer length.

82. (Currently Amended) A method as in claim 81 wherein said mass labels have masses which are different than a mass of each possible ~~amino acid~~ monomer in said set of ~~amino acid~~ monomer sequences.

Appl. No. 10/033,303

**PATENT**

Amdt. dated September 13, 2005

Reply to Office Action of March 9, 2005 and the Notice of  
Non-Compliant Amendment mailed August 25, 2005

83. (Currently Amended) A method as in claim 81 wherein said mass label imparts a unique mass signature to each sequence of said set of ~~amino acid monomer~~ sequences.

84. (Original) A method as in claim 81 wherein said labels are different stable isotopes of the same chemical species.

85. (Currently Amended) A method as in claim 1 wherein said oligomer is ~~[[a]]~~ an oligosaccharide.

86. (Original) A method as in claim 85 wherein said portion of said oligosaccharide is a terminal portion of said oligosaccharide.

87. (Original) A method as in claim 86 wherein said terminal portion is a reducing terminus.

88. (Currently Amended) A method as in claim 86 wherein a label is attached to said ~~portion~~ oligosaccharide.

89. (Original) A method as in claim 88 wherein said label is covalently bonded to said portion prior to generating said mass spectrum data and wherein said mass spectrum data is transformed from an output of a detector plate.

90. (Original) A method as in claim 85 wherein said oligosaccharide is fragmented to generate fragments, comprising said portion, which are then accelerated toward a detector plate to generate said mass spectrum data.

91. (Original) A method as in claim 1 wherein said oligomer is a nucleic acid.

92. (Original) A method as in claim 91 wherein said portion of said nucleic is a terminal portion of said nucleic acid.

Appl. No. 10/033,303

PATENT

Amdt. dated September 13, 2005

Reply to Office Action of March 9, 2005 and the Notice of  
Non-Compliant Amendment mailed August 25, 2005

93. (Original) A method as in claim 92 wherein said terminal portion is 3' terminus.

94. (Original) A method as in claim 92 wherein a label is attached to said portion.

95. (Original) A method as in claim 94 wherein said label is covalently bonded to said portion prior to generating said mass spectrum data and wherein said mass spectrum data is transformed from an output of a detector plate.

96. (Original) A method as in claim 91 wherein said nucleic acid is fragmented to generate fragments, comprising said portion, which are then accelerated toward a detector plate to generate said mass spectrum data.

97. - 103. (Cancelled)

104. (Original) A method as in claim 1 wherein said oligomer is a nucleic acid.

105. - 106. (Cancelled)

107. (Original) A method as in claim 1 wherein said oligomer is labeled prior to being fragmented.

108. (Original) A method as in claim 1 where said oligomer is fragmented and the resulting fragments are labeled.

109. (Original) A method as in claim 104 wherein said portion is a terminal portion of said nucleic acid.

110. (Original) A method as in claim 109 wherein said terminal portion is one of a 3' terminus.

111. (Original) A method as in claim 104 wherein said label is covalently bonded to a primer sequence of a nucleic acid prior to the fragments being generated by Sanger, polymerase chain reaction, or Maxam-Gilbert methods and the generation of mass spectrum data.



Appl. No. 10/033,303

**PATENT**

Amdt. dated September 13, 2005

Reply to Office Action of March 9, 2005 and the Notice of  
Non-Compliant Amendment mailed August 25, 2005

112. (Currently Amended) A method as in claim ~~[[105]]~~ 85 wherein said label is covalently bonded to a reducing terminus of an oligosaccharide ~~prior~~ prior to enzymatic fragmentation of the oligosaccharide and the generation of mass spectrum data.

113. (Currently Amended) A method as in claim ~~[[6]]~~ 115 wherein said protein is fragment by collision-induced-dissociation, either in source or in a collision cell, to generate fragments, comprising said portion, which are then accelerated toward a detector plate to generate said mass spectrum data.

114. (Currently Amended) A method as in claim ~~[[6]]~~ 115 wherein said protein is fragmented by partial exoproteolytic digestion prior to generating the mass spectrum data.

115. (New) A method as in claim 2 wherein said oligomer is a protein.

116. (New) A method as in claim 115, wherein said terminal portion is one of an N-terminal portion or a C-terminal portion.

117. (New) A method as in claim 1, wherein said oligomer is labeled with a labeling moiety comprising at least one mass defect element having an atomic number from 17 to 77.

118. (New) A method as in claim 117, wherein prior to calculating said set of mass/charge ( $m/z$ ) values, said method comprises the steps of:

- (i) discriminating between a mass spectrum peak associated with the labeled oligomer and a mass spectrum peak associated with an unlabeled oligomer, wherein said discriminating is based on the nuclear binding energy of the labeling moiety; and
- (ii) deconvolving the mass spectrum peak associated with the labeled oligomer from the mass spectrum peak associated with the unlabeled oligomer.

119. (New) A method as in claim 1, wherein said oligomer is labeled with a labeling moiety comprising at least one isotope element.

Appl. No. 10/033,303  
Amdt. dated September 13, 2005  
Reply to Office Action of March 9, 2005 and the Notice of  
Non-Compliant Amendment mailed August 25, 2005

PATENT

120. (New) A method as in claim 119, wherein the first ranking calculation and the second ranking calculation comprise an isotope ranking factor.

121. (New) A method as in claim 119, wherein said isotope ranking factor is adapted to rank said set of fragment sequences having the first number of monomers and said set of fragment sequences having the second number of monomers based on the expected abundance of said at least one isotope element.

122. (New) A method as in claim 1, wherein said oligomer is labeled with a labeling moiety comprising at least one isotope element and at least one mass defect element having an atomic number from 17 to 77, wherein

- (1) prior to calculating said set of mass/charge ( $m/z$ ) values, said method comprises the steps of:
  - (i) discriminating between a mass spectrum peak associated with the labeled oligomer and a mass spectrum peak associated with an unlabeled oligomer, wherein said discriminating is based on the nuclear binding energy of the labeling moiety; and
  - (ii) deconvolving the mass spectrum peak associated with the labeled oligomer from the mass spectrum peak associated with the unlabeled oligomer;
- (2) wherein the first ranking calculation and the second ranking calculation comprise an isotope ranking factor adapted to rank said set of fragment sequences having the first number of monomers and said set of fragment sequences having the second number of monomers based on the expected abundance of said at least one isotope element.

123. (New) A machine implemented method for identifying a labeled oligomer fragment in a mass spectrum data of fragments of a labeled oligomer, wherein the labeled oligomer is labeled with a labeling moiety, said labeling moiety comprising at least one mass

Appl. No. 10/033,303

PATENT

Arndt. dated September 13, 2005

Reply to Office Action of March 9, 2005 and the Notice of  
Non-Compliant Amendment mailed August 25, 2005

defect element having an atomic number from 17 to 77, said method comprising the step of discriminating between the mass of the labeled oligomer fragment and the mass of an unlabeled oligomer fragment in said mass spectrum based on the nuclear binding energy of the labeling moiety, thereby identifying said labeled oligomer fragment.

124. (New) A method as in claim 123, wherein said labeling moiety further comprises at least one isotope element.

125. (New) A method as in claim 124, wherein said method further comprises the step of qualifying the mass of the labeled oligomer fragment based on the expected abundance of said at least one isotope element.

126. (New) A method as in claim 123, 122, or 117, wherein said mass defect element is bromine.

127. (New) A method as in claim 126, wherein said at least one isotope element is bromine.

128. (New) A method as in claim 6, wherein said oligomer is fragmented using an enzymatic, chemolytic or mass spectrometric fragmentation method.